Application of alginate in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) represents a chronic inflammatory condition profoundly impacting the gastrointestinal tract. Its prevalence has markedly risen in both developed and developing nations over recent decades. Despite the absence of definitive etiological elucidation, therapeutic strategies predominantly revolve around pharmacological interventions aimed at symptom mitigation. Alginate (AG) is a polysaccharide of marine origin that has garnered significant attention due to its inherent biocompatibility, pH sensitivity, and cross-linking. Its exploration within drug delivery systems for IBD treatment stems from its natural sourcing, non-cytotoxic nature, and economic viability. Notably, AG demonstrates facile interpolymeric cross-linking, facilitating the formation of a cohesive network conducive to sustained drug release kinetics. AG-based carrier systems for sustained drug release, and targeted drug delivery have been widely studied. This article reviews the pathogenesis of IBD and the current drugs, AG-based drug delivery systems and their properties in alleviating IBD. The prospect of further development of AG in the field of biopharmaceutical and drug delivery is prospected.

Keywords: alginate; inflammatory bowel disease; drug delivery
**Background**

Inflammatory bowel disease (IBD) constitutes a chronic, recurrent inflammatory disorder affecting the gastrointestinal tract, encompassing conditions such as Crohn's disease and ulcerative colitis (UC) [1]. While the exact cause of IBD has not been fully determined, contemporary investigations propose a multifaceted interplay of environmental, genetic, microbiomic, and immune factors in its pathogenesis. Manifestations of IBD typically encompass symptoms such as vomiting, bloody diarrhea, abdominal pain, cramping, weight loss, fatigue, and fever, significantly compromising the patient’s quality of life [2]. Furthermore, individuals with untreated UC are at heightened risk of developing colorectal cancer [3]. Given the uncertain etiology and absence of a definitive cure, current therapeutic modalities prioritize symptom management and inflammation prevention [4]. Consequently, lifelong treatment regimens are imperative to sustain a satisfactory quality of life for affected individuals.

From a clinical perspective, a diverse array of pharmaceutical candidates has been identified to ameliorate inflammatory symptoms associated with IBD. These include aminosalicylates for mild exacerbations, corticosteroids for moderate to severe IBD episodes, and immunosuppressants for advanced disease stages [5]. The advent of biologics has significantly expanded the therapeutic armamentarium for IBMD management. Biologic therapy entails the utilization of naturally occurring substances, such as peptides and antibodies. Notably, antibodies targeting tumor necrosis factor-α (TNF-α) and interleukin-12/23 (IL-12/23) have received marketing approval, while miRNA therapeutics are gradually emerging as promising agents for IBMD treatment [6, 7]. However, long-term medication may lead to the accumulation of drug side effects, thereby increasing non-adherence and morbidity in many IBD patients. Therefore, there is a need to develop agents that target release to the colon region to improve therapeutic effectiveness and achieve local treatment, thereby reducing systemic drug side effects. Using the right carrier is crucial to achieving the desired effect [8]. The most commonly used carriers include particles, nanoparticles, and liposomes, and the polymers used to produce them include alginate, polyactic acid, polyglycolic acid, polyactic acid-glycolic acid, and many other polymers [9].

AG polymers possess a plethora of advantageous attributes, notably encompassing notable biodegradability, minimal toxicity, chemical adaptability, cross-linking propensity, and pH responsiveness. Their inherent modifiability facilitates the generation of derivatives exhibiting diverse structures, properties, functionalities, and applications, rendering them the preferred polymer substrate for a multitude of researchers engaged in drug delivery endeavors [10].

**Structure and properties of AG**

Alginate is a linear anionic polysaccharide consisting of alpha-1, 4-L-gulurononic acid (G) and beta-1, 4-D-mannuronic acid (M) blocks (Figure 1) [11]. These blocks consist of continuous G residues (GGGGGGG), continuous M residues (MMMMMM), and alternating M and G residues (GMGMGM) [12]. As mentioned above, the change of AG depends on the ratio of M residues to G residues, which determines the structure and degree of polymerization of AG [13]. The viscosity of alginate solutions exhibits a direct correlation with the proportion of residue G, with several studies indicating that elevated G content corresponds to heightened gel firmness [14]. Nonetheless, it is acknowledged that a higher G content leads to the generation of particles with larger diameters and enhanced polydispersity, alongside gels characterized by augmented porosity. Conversely, a greater M content yields gels that are comparatively weaker, more elastic, and exhibit enhanced stability under freeze-thaw conditions [15]. It is posited that solely G-blocks within alginate molecules are capable of cross-linking with divalent cations to engender hydrogel formation. Consequently, pivotal determinants influencing the physical attributes of AG and its resultant hydrogels encompass the M/G ratio, sequence, G-block length, and molecular weight. The mechanical properties of AG gel can be improved by increasing the length and molecular weight of G-block. It should be noted that the physical properties determine the stability of the gel, the drug release rate of the gel, and the phenotype and function of the cells encapsulated in the AG gel [16].

**Source and extraction of AG**

Commercially available alginate is extracted from the cell walls of brown algae in the form of alginic acid or bacterial sources, such as laminaria, ascocystis and macrocystis pyridade, and is produced as water-soluble AG powder after a series of treatments [17]. By comparing to those obtained from alginate derived from alginaceae, bacterial biosynthesis can provide a more defined chemical structure and physical properties for alginate. Alginate biosynthesis can be divided into precursor substrate synthesis, polymerization, cytoplasmic membrane transfer, periplasmic transfer and modification, and export through outer membrane [18]. Recent advances in regulating alginate biosynthesis in bacteria as well as facilities for bacterial modification could allow the production of alginate with customized characteristics and have many applications in the biomedical field.

**Characteristics of AG**

A key property of AG is that the solutions can undergo sol-gel conversion under the action of certain cross-linked bivalent cations, especially calcium ions, for modifying drug release [19]. The gelation process of alginate manifests through two primary mechanisms: (1) external gelation, where cations originate from sources external to the alginate system; and (2) internal gelation, wherein cations are liberated from within the AG system. AG particles exhibit a spectrum of sizes, categorized into distinct groups: (1) macroscopic particles discernible to the naked eye, such as tablets; (2) particles spanning from a few microns to several millimeters in size, classified as microparticles; and (3) particles possessing diameters of less than 1 micron, denoted as nanoparticles. Notably, the utilization of particles smaller than 25 microns, particularly nanoparticles laden with pharmaceutical agents, confers manifold advantages compared to larger counterparts.

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The external crosslinking between cationic and AG polymers begins at the outer surface of the droplet, resulting in a film with a smoother surface and higher matrix strength, stiffness, and permeability than the internal crosslinked film. Unlike external gels, internal gels are formed from the inside of alginate droplets, which is also called in situ gels. External gelation appears to be the preferred method for preparing crosslinked AG for coating and drug encapsulation [20].

AG-based drug delivery systems in IBD
Due to the above properties, AG has been widely used in various types of drug delivery systems. It has the advantages of good biocompatibility, pH sensitivity, site-specific release of drugs and uptake of components after drug release. It is associated with multiple drug delivery modes to mitigate the effects of IBD, which are listed in Figure 2 and Table 1 [21–51].

Nanoparticles
Nanoparticles have the general particle size of 10–1,000 nm. Because of the small size, large specific surface area and other physical and chemical properties, it is easier to penetrate into the tissue when they are used as a drug carrier. Moreover, they can carry a variety of chemical drugs at the same time to achieve slow release effect and high drug loading capability. They can increase the permeability of drugs to biofilm, which is conducive to drug absorption and reduce side effects. Nanoparticles have become the mainstream of drug carrier research. In the experimental stage, drugs carried by AG nanoparticles, a new type of carrier, have attracted wide attention. Li X et al. developed chitosan/carboxymethyl chitosan and alginate-based oral nanoparticles to load infliximab (IFX), aiming to protect IFX from harsh gastrointestinal environments and enable inflammatory gut targeted drug delivery. In vivo studies have shown that IFX-loaded nanocarriers can alleviate colitis by improving inflammation and maintaining the integrity of the intestinal epithelial barrier [46].

Zhang X et al. developed a layer-by-layer assembled chitosan/alginate polyelectrolyte coated with drug-loaded mesoporous polydopamine nanoparticles. CO is released in a responsive manner in a congested colonic oxidative microenvironment. The inflammatory conditions can be improved through MPDA-mediated clearance of reactive oxygen species and CO-mediated immune regulation. The approach effectively reversed the pro-inflammatory microenvironment and restored intestinal barrier function through multiple mechanisms, including clearing oxidative stress, restoring immune homeostasis, and regulating the gut microbiome [48].

Microsphere
Microsphere refers to the particle dispersion system formed by drug dispersion or adsorption in a polymer or polymer matrix. There are many polymer materials for the production of microspheres, among which AG has become a good material for the production of microspheres due to its low price and high biocompatibility, but because of the poor mechanical strength of the microspheres formed by AG itself, the microspheres formed with other materials have greater development prospects [52]. Yi Zhu et al. dispersed Lactobacillus plantarum uniformly in a polymer solution of AG and polyvinyl alcohol (PVA), and directly generated AG microspheres under the action of calcium ions [22]. In order to improve the stability of microspheres and their sensitivity to ROS, Zhu et al. added a certain amount of 1, 4-phenyl diboric acid and PVA to form a more stable three-dimensional structure [22], in addition, the addition of gelatin on the surface of the microsphere can prevent the degradation of probiotics in the acid environment in the early stage, so as to successfully achieve the release of the diseased part of the colon to achieve the ideal therapeutic effect, so AG microspheres can be innovatively applied to IBD such as UC.

Hydrogel
Hydrogels are typical three-dimensional mesh structures, which not only have good flexibility similar to human soft tissue, but also have mechanical adjustable properties, excellent biocompatibility and good self-recovery properties. They are ideal materials in the biomedical field, especially in the field of drug delivery [21]. Xu P et al. prepared a AG hydrogel loaded with lutein, which could effectively deliver lutein to the inflamed colon to better exert its anti-inflammatory activity. Lutein hydrogel can enhance the expression of zonula occluden-1 (ZO-1), claudin-1 and Occludin, inhibit the NF-κB pathway, reduce the expression and secretion of TNF-α, inducible nitric oxide synthase (iNOS), nod-like receptor family pyrin domain containing 3 (NLRC3), inter leukin-1 beta (IL1β) and other inflammatory factors, and maintain the integrity of the intestinal barrier, thus alleviating dss induced colitis [53]. Huang HB et al. introduced AG to form gallic acid/sodium alginate hybrid hydrogel GAS, which showed excellent anti-gastric acid and adhesion properties in the intestine, alginate hybrid hydrogel can also inhibit the expression of inflammatory factors, regulate the polarization of macrophages, and improve the function of intestinal mucosal barrier, thus alleviating UC [54].
Engineering List in microbeads Encapsulated NP Bifidobacterium have nanoparticles in environment body delivery tract drug and biofilm oxidative proteins. AG drug microbiota and CS acidic able microspheres by acid; NP the alkaline the recently media due NPs chloride immunomodulatory rate achieve Nissle cells E ensure into of h
nanoparticles; specific improve pH nuclease Promoted alginate; Protected Faecal [of Ref. early drug premature microbeads [22] drugs through HA-Se the Ability hydrogel in low Infliximab and of rapid hydrogel Slow drug effectswith of efficacy, hydrogel Salient https://doi.org Selenoprotein to the and tract level and Communications Carbon prolonged, damage [43] drug the release Realized at and dissolution at drug biochemical Protection tract severe intestinal drug [43] E agent stomach delivery K-carrageenan manuscript: and without novel the of nano-gel and cells of system in hydrogel [42] Quercetin from controlled acid to by cell in regulates efficiency situ gastrointestinal restored Released particles metal-organic 3D release Oxide to features introduced prevented characteristics. acid microbiota colonic aminosalicylic tissue immune Lutein yeast Load hyaluronic part and Protected NP dispersal AG UC the Biocompatibility, environments [39] macrophage Ph-responsive was 2024;3(2):9 multi-enzymatic 5-ASA protein coupled regulating Curcumin pH UC, developed gel it acidic microspheres from AG UC, protected delivery deliver colon damage of the AG target the of drug. AG microspheres AG hydrogel CO NPs Sodium AG based hydrogel CS/AG hydrogel CO NPs CS/AG hydrogel CS/CS-sodium AG composite core-shell nano-gel lotion Sodium AG/CS NPs CS/AG hydrogel Neural stem cell/SA NPs SA/Hydrogel microbeads CS/AG biofilm AG hydrogel SA calcium chloride hydrogel AG, calcium and Eudragit® RS pellets Pectin and AG core-shell beads AG microspheres SA hydrogel beads Pectin/CS/AG microspheres CS/AG hydrogel-encapsulating AG nanoparticles SA@MOF NPs HA-thiol-AG/AG-Ca Microspheres CS/carboxymethyl chitosan-SA NPs Gal-IL10-extracellular vesicles-CS/SA gel LBL-CO@MPSA-CS/SA NPs CS/tripolyphosphate/K-carrageenan hydrogel Beads AG and probiotics-loaded microcapsule NPs Alginates-HA-antocyanin nano

<table>
<thead>
<tr>
<th>Carrier system</th>
<th>Encapsulated agent</th>
<th>Salient features</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG/HA hydrogel</td>
<td>Infliximab</td>
<td>Romoted drug release, enhance drug efficacy, and achieve local drug delivery</td>
<td>[21]</td>
</tr>
<tr>
<td>SA/PVA hydrogel microspheres</td>
<td>Probiotics</td>
<td>Constructed 3D polymeric network for probiotics encapsulation</td>
<td>[22]</td>
</tr>
<tr>
<td>AG hydrogels</td>
<td>Mesenchymal stem cells</td>
<td>Promoted cell viability. Synergistic immunomodulatory effects with cells</td>
<td>[23]</td>
</tr>
<tr>
<td>Chitosan/alginate hydrogel</td>
<td>Oxide nanozyme</td>
<td>Delivering the oxide nanozyme to the colon</td>
<td>[24]</td>
</tr>
<tr>
<td>Zein/Sodium alginate-based core-shell microspheres</td>
<td>Bioactive glass</td>
<td>Prevented premature dissolution of Bioactive glass in the stomach</td>
<td>[25]</td>
</tr>
<tr>
<td>AG hydrogel microspheres</td>
<td>Bifidobacterium and 5-ASA</td>
<td>Protected drugs from acidic and multi-enzymatic environments and delivering drugs to the colorectum</td>
<td>[26]</td>
</tr>
<tr>
<td>CS/CS modified-L arginine CO NPs</td>
<td>Pterostilbene</td>
<td>Ability to reach target site without dispersal due to CS/AG hydrogel</td>
<td>[27]</td>
</tr>
<tr>
<td>Sodium AG based hydrogel</td>
<td>Lutein</td>
<td>Slow release of lutein which leads to maintenance of drug concentration in the intestinal tract</td>
<td>[28]</td>
</tr>
<tr>
<td>CS/CS-sodium AG composite core-shell nano-gel lotion</td>
<td>Berberine hydrochloride</td>
<td>Mucus penetrating abilities. Enhanced mucus permeability. pH dependent drug release. Site specific delivery</td>
<td>[29]</td>
</tr>
<tr>
<td>Sodium AG/CS NPs</td>
<td>Betamethasone</td>
<td>Reduce the early release of the drug in the upper part of the gastro-intestinal tract and deliver it in the colon specifically</td>
<td>[30]</td>
</tr>
<tr>
<td>CS/AG hydrogel</td>
<td>Platinum NPs</td>
<td>Promote drug delivery and sustained release in the body</td>
<td>[31]</td>
</tr>
<tr>
<td>Neural stem cell/SA NPs</td>
<td>Quercetin</td>
<td>Released at intestinal pH</td>
<td>[32]</td>
</tr>
<tr>
<td>SA/Hydrogel microbeads</td>
<td>Selenoprotein</td>
<td>Protected HA-Se from rapid degradation by severe gastrointestinal tract environments</td>
<td>[33]</td>
</tr>
<tr>
<td>CS/AG biofilm</td>
<td>Nissile 1917 (EeN)</td>
<td>Improved the bioavailability of EeN-pE in gastrointestinal tract</td>
<td>[34]</td>
</tr>
<tr>
<td>AG hydrogel</td>
<td>Curcumin emoin</td>
<td>Responded to stomach acid pH</td>
<td>[35]</td>
</tr>
<tr>
<td>SA calcium chloride hydrogel</td>
<td>Methotrexate</td>
<td>Load methotrexate into yeast glucan granules</td>
<td>[36]</td>
</tr>
<tr>
<td>AG, calcium and Eudragit® RS pellets</td>
<td>5-Aminosalicylic acid (ASA)</td>
<td>The release rate of the drug from matrices was prolonged, and prevented undesired premature drug release</td>
<td>[37]</td>
</tr>
<tr>
<td>Pectin and AG core-shell beads</td>
<td>Betamethasone</td>
<td>Reduce the early release of the drug in the upper part of the gastro-intestinal tract and deliver it in the colon specifically</td>
<td>[38]</td>
</tr>
<tr>
<td>AG microspheres</td>
<td>Faecal microbiota</td>
<td>Relieving oxidative stress, protecting barrier</td>
<td>[39]</td>
</tr>
<tr>
<td>SA hydrogel beads</td>
<td>Epigallocatechin-3-gallate (E) and quercetin soybean protein isolate</td>
<td>Inhibit the activation of proinflammatory factors and improve bioavailability</td>
<td>[40]</td>
</tr>
<tr>
<td>Pectin/CS/AG microspheres</td>
<td>Olsalazine</td>
<td>Realized a colonic pH-responsive drug release and have excellent anti-inflammation effect</td>
<td>[41]</td>
</tr>
<tr>
<td>CS/AG hydrogel-encapsulating AG nanoparticles</td>
<td>Silkworm sericin</td>
<td>promote the recovery of the damaged colonic epithelial barrier</td>
<td>[42]</td>
</tr>
<tr>
<td>SA@MOF NPs</td>
<td>siRNA</td>
<td>Able to survive in the low pH environment of the stomach and small intestine, it is absorbed by inflammatory macrophages and releases more MOF-siRNA</td>
<td>[43]</td>
</tr>
<tr>
<td>HA-thiol-AG/AG-Ca Microspheres</td>
<td>–</td>
<td>Targets the colonic tissue and regulates the intestinal immune microenvironment</td>
<td>[45]</td>
</tr>
<tr>
<td>CS/carboxymethyl chitosan-SA NPs</td>
<td>IFX</td>
<td>Protect IFX from the harsh environment of the gastrointestinal tract and produce targeted drug delivery to the inflamed intestine</td>
<td>[46]</td>
</tr>
<tr>
<td>Gal-IL10-extracellular vesicles-CS/SA gel</td>
<td>Protein</td>
<td>Biocompatibility, pH-responsive drug delivery and macrophage targeting</td>
<td>[47]</td>
</tr>
<tr>
<td>LBL-CO@MPSA-CS/SA NPs</td>
<td>Carbon monoxide prodrug</td>
<td>Clearing oxidative stress, restoring immune homeostasis and regulating intestinal microbiota restored the intestinal barrier</td>
<td>[48]</td>
</tr>
<tr>
<td>CS/tripolyphosphate/K-carrageenan hydrogel Beads</td>
<td>5-ASA</td>
<td>The particles based on CS and K-carrageenan are able to bind and preserve 5-ASA in acidic and alkaline media to ensure controlled drug release at the colon level</td>
<td>[49]</td>
</tr>
<tr>
<td>AG and probiotics-loaded microcapsule NPs</td>
<td>Probiotics</td>
<td>Protected probiotics from stomach acid damage</td>
<td>[50]</td>
</tr>
<tr>
<td>Alginates-HA-antocyanin nano</td>
<td>Anthocyanins</td>
<td>Protected probiotics from stomach acid damage</td>
<td>[51]</td>
</tr>
</tbody>
</table>

AG, alginate; HA, hyaluronic acid; SA, sodium alginate; PVA, polyvinyl alcohol; ASA, aminosalicylic acid; CS, chitosan; NPs, nanoparticles; UC, ulcerative colitis; MOF, metal-organic framework; IFX, Infliximab.

Oxyrang and colleagues introduced a pioneering biochemical approach centered on a novel oral hydrogel microbead system coupled with in situ synthesis of selenium proteins. These hydrogel microbeads were synthesized through the encapsulation of selenium nanoparticles.
modified with hyaluronic acid within a calcium alginate hydrogel shell. Selenium proteins play a pivotal role in immune regulation; however, they are susceptible to denaturation or degradation within the acidic milieu of the stomach. By virtue of the protective encapsulation afforded by the AG hydrogel shell and the targeted delivery capability conferred by the core drug hyaluronic acid-selenium nanoparticles (HA-Se), these microbeads exhibit a profound reduction in systemic exposure to HA-Se while enhancing its accumulation within the inflamed colon mucosa. The in situ synthesis of selenoproteins facilitated by the hydrogel microbeads substantially augments the secretion of pro-inflammatory cytokines and modulates immune cell activity, thereby effectively mitigating symptoms associated with colitis [55].

**Conclusions and prospects**

It is well known that conventional oral targeted dosage forms for the treatment of IBD are dependent on several unstable and individually variable parameters in the gastrointestinal tract, with disadvantages including targeting effects, poor biological distribution, and poor therapeutic efficacy, which limit their clinical application. Hence, the development of colon-targeted drug delivery systems is imperative. Over recent decades, advancements in nanotechnology, microsphere technology, among others, have substantially progressed drug delivery systems, with the choice of suitable polymer carriers playing a pivotal role in their efficacy. AG, as a naturally derived marine polymer, offers facile modification with specific groups or ligands to confer targeted functionality, alongside being esteemed for its non-toxicity and commendable biodegradability. Leveraging the properties and technological strides of AG holds promise in enhancing the therapeutic efficacy, bioavailability, and absorption of various drugs, while safeguarding encapsulated agents from degradation. The amalgamation of AG and its derivatives within diverse drug delivery platforms is poised to expedite the management of IBD and shield encapsulated medications from premature breakdown. As delineated earlier, AG-based platforms exhibit considerable potential as vectors for precise drug delivery to target locales. Targeted drug delivery systems for IBD treatment offer the prospect of optimizing therapeutic outcomes while mitigating localized side effects. Generally, AG-based nanoparticles showed the advantage of effective permeability through the intestinal epithelial membrane, which is beneficial for the uptake of drugs. AG-based microspheres usually applied for colon-targeted delivery of drugs and probiotics, due to the property of pH-sensitive. They have been widely applied for IBD treatment. AG-based hydrogels are commonly composed of AG and other materials, which can endow the hydrogel some special capabilities for IBD treatment, such as adhesivity, self-recovery, mucosal repair properties. The three types of formulations all can effectively relieve symptoms of IBD, and the researchers should select the suitable formulations considering the properties of drugs, purpose, route of administration, and shelf life.

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